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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/263,689	Applicant(s) Ni et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *90-114, 116-120, and 128-131* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *90-114, 116-120, and 128-131* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *30*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 121, 124-127, 132, 133 and 136-140 have been canceled. Claims 90-114, 116-120, 128-131 are pending and under consideration.

3. The rejection of claims 90-114, 116-120, and 128-131 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well-established utility is maintained for reasons of record. Applicants argues that the post-filing date reference of Sato et al teaching that the galectin 9 isoform which is identical to the instant SEQ ID NO:4 has the same ECA activity as galectin 9 and is therefore useful in the detection of asthma. However, the specification fails to teach a correlation between ECA activity and asthma. It is also noted that the Hirashima et al (2000) reference which teaches the correlation between ECA and asthma was also a post-filing date reference. It is noted that the therapeutic uses set forth in the references published after the instant filing cannot be relied upon for enablement of the instant specification, as what is known in the art after the instant filing date is of no consequence regarding what one of skill in the art believed as of the filing date. See In re Wright, 27 USPQ 1510, 1514 (Fed. Cir. 1993).

4. In light of the above, the rejection of claims 90-114, 116-120, and 128-131 under 35 U.S.C. 112, first paragraph, because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility is maintained..

5. In the event that Applicants might be able to overcome the 35 U.S.C. 101 rejection above, the following rejection would be applied:

6. Claims 90, 92, 94-98, 100, 102-114, 116-120, 128-131, 133 and 136-140 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the polypeptides comprising SEQ ID NO:4 and polypeptides consisting of amino acids 62-102, 226-259 and 197-308 of SEQ ID NO:4, does not reasonably provide enablement for polypeptides comprising 30 or 50 contiguous amino acids of SEQ ID NO:4, polypeptides comprising amino acids 62-102, 226-259 and 197-308 of SEQ ID NO:4, proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4 or proteins comprising amino acids which are encoded by polynucleotides that hybridize to SEQ ID NO:3 or the complement thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record set forth in the Office action of Paper No. 14 and for the further reasons stated below.

(A)As drawn to proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4

Claims 90, 92, 94-98, 100, 102-105, 128, 129 are drawn to proteins comprising polypeptide variants of SEQ ID NO:4 which bind lactose. Carbohydrate binding domains are recognized in the art (figure 2 of Tureci et al). Although one of skill in the art could generate variants to SEQ ID NO:4 which would not eliminate the lactose binding of the resultant peptide, the effect of alterations of the amino acid sequence in the non-carbohydrate binding portion of SEQ ID NO:4 cannot be anticipated. The relationship between primary amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (ibid), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. (Lazar et al, ibid). These references demonstrate that even a single amino acid substitution or what appears to be a small chemical modification will often dramatically affect the biological activity and characteristic of a protein, and the specification gives no guidance on or exemplification of how to make/use the broadly claimed variant polypeptides.

Applicant argues that the amendment of the claims to specify lactose-binding ability renders moot the rejection under 35 U.S.C. 112, first paragraph. Enablement under 112, first paragraph is based on having a specific and substantial use. As all galectins bind lactose, this function is not specific. Hirashima (2000) teaches that recombinant proteins consisting of the N-

terminal carbohydrate binding region or the C-terminal carbohydrate binding region of ecalectin exhibited 100-fold less eosinophilic attractant activity in contrast to wild-type ecalectin. Hirashima teaches that a combination of the N-terminal and C-terminal fragments did not reconstitute the eosinophil chemo attractant activity of ecalectin (page 7, second column lines 4-8). Hirashima concludes "From these results, it is suggested that divalent galactoside binding activity is required for eosinophile chemo attraction by ecalectin, and that it is not sufficient to exhibit ECA activity (eosinophil chemo attraction)" (page 7, second column, lines 22-26). Therefore Hirashima teaches that lactose-binding ability is a necessary but not sufficient requirement for eosinophilic chemo attraction. The binding of lactose therefore, cannot be considered a substantial because, as an isolated protein function, it is not key to the eosinophilic chemo attraction activity of ecalectin.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the variant polypeptides of SEQ ID NO:4 as amendment of the claims to recite lactose binding ability does not narrow the scope of the claims to allow one of skill in the art to practice the claimed invention without undue experimentation.

(B)As drawn to proteins comprising fragments of SEQ ID NO:4

Claims 106-113 and 130 are drawn to isolated proteins comprising amino acid residues 62-102, 226-259, and 197-308 having lactose binding activity. The specification teaches that the fragments of SEQ ID NO:4 consisting of amino acid residues 62-102, 226-259 and 197-308 are

antigenic epitopes of SEQ ID NO:4. The specification defines "antigenic epitopes" on page 26, lines 1-2, as "a region of a protein molecule to which an antibody can bind" and differentiates said antigenic epitopes from immunogenic epitopes (page 25, lines 25-30). It is noted that the specification does not teach that these fragments are responsible for lactose-binding activity. The claims, however, are drawn to proteins comprising said epitopes and it cannot be predicted that these sequences, when embedded into a different amino acid context, would still be accessible to reaction with antibodies. Paul (Fundamental Immunology, (text), 1993, pg. 249, column 2, lines 9-17) teaches that accessibility of an antigenic determinant on the surface of the protein is necessary for the antigenic determinant to be bound by the antibody. Paul states that knowledge of the three-dimensional structure is necessary to predict such accessibility. In addition, Paul states that mobility of the putative antigenic determinant within the protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Given the broadest reasonable interpretation claims 106-113 read on any protein having lactose binding ability comprising the recited amino acid residues. The scope of the claims must be commensurate with the scope of the enablement set forth, and with the exception of the antigenic regions of SEQ ID NO:4 consisting of amino acid residues 62-102, 226-259 and 197-308, the specification gives no guidance on or exemplification of how to use the polynucleotides that encode the broadly claimed polypeptides having lactose binding ability. Given that state of the art with regard to protein chemistry and antigenic determinants as set forth above, and the lack of teachings in the

specification, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

Claims 114, 116-120 and 131 are drawn to proteins which consist of at least 30 contiguous amino acids of SEQ ID NO:4. Applicant has amended claim 114 in order to obivate the following rejection, however, "consisting of at least" is open language due to the "at least". When given the broadest reasonable interpretation, the claim can read on proteins comprising 30 contiguous amino acids in addition to heterologous sequence. The specification does not demonstrate that insertion of fragments of the putative SEQ ID NO:4 into a different amino acid context would result in a polypeptide having the asserted utility of being diagnostic for Hodgkin' disease or asthma. Even if SEQ ID NO:4 was specifically correlated to Hodgkin's disease or asthma, it cannot be anticipated that peptides comprising fragments of SEQ ID NO:4 would have the same use or expression as SEQ ID NO:4. The art teaches that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1,). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the SEQ ID NO:4 polypeptide can potentially profoundly alter the three dimensional structural environment in which the given fragment is located

(Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem", page 6, second column, first paragraph, In:Perspectives in Biochemistry, Vol. 1, pp. 6-9,). Thus, the consequences of the altered sequence environment on the fragment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects, such as membrane anchorage, protein activation and sub-cellular location must be considered with respect to protein function in addition to molecular aspects (Bork, p. 398, col 2). Given the state of the art regarding the relationship between primary amino acid sequence, structure and function of proteins, and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed proteins.

7. All other rejections and objections as stated in Paper No. 27 are withdrawn.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

January 13, 2003

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